PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/005626	22.02.2005	20.02.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/40, A61P9/12

Applicant
THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/005626

[illegible] 18 AUG 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-13 (IA)

because:

☒ the said international application, or the said claims Nos. 1-13 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	14-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	14-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

10/588673
IAP20 Rec'd PCT/PTO 08 AUG 2006

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2005/005626

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: TAKAHASHI KOKI ET AL: "Enhanced activities and gene expression of phosphodiesterase types 3 and 4 in pressure-induced congestive heart failure" HEART AND VESSELS, SPRINGER, BERLIN, DE, vol. 16, no. 6, September 2002 (2002-09), pages 249-256, XP002278931 ISSN: 0910-8327

D2: TSUBOI YASUSHI ET AL: "Suppression of mesangial proliferative glomerulonephritis development in rats by inhibitors of cAMP phosphodiesterase isozymes types III and IV" JOURNAL OF CLINICAL INVESTIGATION, vol. 98, no. 2, 1996, pages 262-270, XP002330144 ISSN: 0021-9738

D3: US-A-5 286 494 (FECHNER ET AL) 15 February 1994 (1994-02-15)

D4: KARPPANEN H ET AL: "Central hypotensive effects of imidazole acetic acid and rolipram (ZK 62 711) in rats" AGENTS AND ACTIONS 1979 SWITZERLAND, vol. 9, no. 1, 1979, pages 84-86, XP009048338

D5: JUNG A ET AL: "Evidence that phosphodiesterase 4b plays a mechanistic role in salt-adaptation and is a therapeutic target for hypertension in the dahl rat" AMERICAN JOURNAL OF HYPERTENSION, ELSEVIER, vol. 17, no. 5, May 2004 (2004-05), page S90, XP004575635 ISSN: 0895-7061

If not mentioned otherwise, the relevant passages are those mentioned in the International Search Report.
cAssuming a valid priority of the present application the P-document cited in the International Search Report (D5) is not dealt with during the PCT-phase.

Art 33(2) The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of claims 14-17 is not new. Claims 14-17 are drafted as composition claims. Hence, the subject matter of claims 14-17 discloses nothing more than the compositions *per se*.
D3 discloses pharmaceutical compositions comprising rolipram. Therefore, the subject-matter of claims 14-17 is not new in the light of D3.

The subject-matter of claims 1-13 is new in the sense of Article 33(2) PCT. Prior art does not disclose the use of a phosphodiesterase inhibitor for the treatment of salt-sensitive hypertension.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 1-13 does not seem to involve an inventive step.
D2 discloses that inhibition of PDE4 by rolipram lowers systolic blood pressure. The problem to be solved by the present invention may therefore be regarded as how to provide another medical use of a phosphodiesterase inhibitor.
The present application suggests to solve the problem posed by using an inhibitor of phosphodiesterase (in particular of PDE4B1 and PDE4D5, e.g. rolipram) in the treatment of salt sensitive hypertension.
D1 discloses that PDE 4 activity is enhanced in salt sensitive hypertension and suggests inhibition of PDE4 as treatment in order to avoid hypertension-induced congestitive heart failure. D4 discloses that rolipram dose-dependently reduces blood pressure.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of claims 14-17 the applicant's attention is drawn to the fact that even if novelty could be established over the above-cited prior art it is at present not clear wherein an inventive step may reside.

With respect to the subject-matter of claims 1-13 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel result in a solution of the posed problem which could not have been foreseen by the skilled person. Present claims 1-13 claim the use of *inter alia* rolipram in the treatment of a patient group characterized by having a salt-sensitive arterial hypertension, i.e. a subgroup of patients suffering from hypertension.
To arrive at the present subject-matter, the skilled person perfomed an arbitrary choice out of one list containing all different types of hypertension to select salt-sensitive hypertension. Although not necessessary to perform an arbitrary choice, the teaching of D1 even directed the skilled man towards that choice. Present figures 1A and 1B clearly demonstrate that rolipram is efficient in dipping arterial blood pressure both in SHR and salt-sensitive rats, i.e. in all forms of hypertension being investigated.
Consequently, there is no surprising effect resulting from said choice and, therefore, the solution proposed in claims 1-13 of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

It is therefore noted, that the solution proposed in claims 1-17 of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

Art 33(4) For the assessment of the present claims 1-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-

matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The subject-matter of claims 14-17 is considered to be industrially applicable in the sense of Art 33(4) PCT.

Re Item VI
Certain documents cited

D5 discloses the efficacy of rolipram in reducing salt-sensitive hypertension. The authors conclude that PDE4B is a therapeutic target for treating salt-sensitive hypertension.